

# Hepatitis C

## Surveillance Protocol

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### Provider Responsibilities

- 1) Report newly diagnosed persons with acute hepatitis C by completing the provider and laboratory (yellow and green) sections of the WVEDSS form. Forward the completed WVEDSS form and the laboratory report to the Infectious Disease Epidemiology Program (350 Capitol St, Room 125; Charleston, WV 25301). Include all of the following information:
  - a) Patient name, date of birth, address and phone number
  - b) Demographic information including race, sex, age, and ethnicity.
  - c) Symptoms: did the patient have symptoms of acute hepatitis C?
  - d) Laboratory results, including:
    - i) Hepatitis A IgM, if done;
    - ii) HBsAg and Anti-HBc IgM, if done;
    - iii) Hepatitis C screening test i.e.:
      - (1) Enzyme Immunoassay (EIA) or
      - (2) Enhanced chemiluminescence immunoassay (CIA) and
    - iv) Confirmatory testing, i.e.:
      - (1) Signal-to-cutoff ratio for screening test; or
      - (2) Recombinant Immunoblot Assay (RIBA); or
      - (3) Polymerase chain reaction (PCR); and
    - v) Other positive results (e.g., quantitative nucleic acid test results or genotype); and
    - vi) Bilirubin; and
    - vii) Transaminase levels.
- 2) Educate newly diagnosed persons about hepatitis C, especially ways to reduce transmission. The WVDHHR 'Information for the Public' is available for this purpose.
- 3) Educate patients about appropriate screening recommendations. These are from CDC at <http://www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm>

PERSONS	RISK OF INFECTION	TESTING RECOMMENDED?
Injecting drug users	High	Yes
Recipients of clotting factors made before 1987	High	Yes
Hemodialysis patients	Intermediate	Yes
Recipients of blood and/or solid organs before 1992	Intermediate	Yes

### Infectious Disease Epidemiology Program

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PERSONS	RISK OF INFECTION	TESTING RECOMMENDED?
People with undiagnosed liver problems	Intermediate	Yes
Infants born to infected mothers	Intermediate	After 12-18 mos. old
Healthcare/public safety workers	Low	Only after known exposure
People having sex with multiple partners	Low	No*
People having sex with an infected steady partner	Low	No*

\*Anyone who wants to get tested should discuss with their doctor.

### **Laboratory Responsibilities**

- 1) Forward paper copies of positive laboratory results for hepatitis C to the Infectious Disease Epidemiology Program (350 Capitol St, Room 125; Charleston, WV 25301) within one week. Please include:
  - a) Full name, date of birth, address and phone number;
  - b) Demographic information including age, sex, race and ethnicity, if available;
  - c) Full physician name, address and phone number; and
  - d) Laboratory results, normal values and interpretation, including:
    - i) Hepatitis A IgM, if done;
    - ii) HBsAg and Anti-HBc IgM, if done;
    - iii) Hepatitis C screening test i.e.:
      - (1) Enzyme Immunoassay (EIA) or
      - (2) Enhanced chemiluminescence immunoassay (CIA) and
    - iv) Confirmatory testing, i.e.:
      - (1) Signal-to-cutoff ration for screening test; or
      - (2) Recombinant Immunoblot Assay (RIBA); or
      - (3) Polymerase chain reaction (PCR); and
    - v) Other positive results (e.g., quantitative nucleic acid test results or genotype); and
    - vi) Bilirubin, if done; and
    - vii) Transaminase levels, if done.
- 2) All laboratories should perform and report results of reflex supplemental testing if screening test for anti-HCV is positive (MMWR February 7,2003, vol. 52, No. RR-3).

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### **Public Health Action**

- 1) Educate the general public about:
  - a) Hepatitis C risk factors and
  - b) Prevention of hepatitis C transmission.
- 2) Educate providers about
  - a) Reporting of newly diagnosed acute hepatitis C through WVEDSS.
- 3) Educate laboratories and providers to report any positive test for hepatitis C to the Infectious Disease Epidemiology Program (IDEP), West Virginia Bureau for Public Health (WVBPH) within one week.
- 4) Educate correctional facilities about recommendations in the MMWR January 24, 2003/ Vol. 52/ No. RR-1, as follows:
  - a) Evaluate inmate risk factors for HCV infection during the entry medical evaluation, and test inmates reporting risk factors for HCV.
    - i) Do appropriate diagnostic testing to differentiate acute hepatitis A, B or C for inmates with signs and symptoms of acute hepatitis and determine if the patient has chronic HBV or HCV infection.
    - ii) Report cases of acute and chronic (past or present) hepatitis C to the Infectious Disease Epidemiology Program at West Virginia Bureau for Public Health.
  - b) Do prompt epidemiologic investigation in collaboration with the public health authorities to identify the source of the infection for all inmates with acute hepatitis C, including those incarcerated >6 months.
- 5) When a Hepatitis C Case Report is received, evaluate to determine if the case meets the acute case definition by checking the following information:
  - a) Does the patient have signs and symptoms of hepatitis?
  - b) Is the patient's alanine aminotransaminase (ALT) or serum glutamic-pyruvic transaminase (SGPT) level more than 400 IU/mL?
  - c) Does the patient have:
    - i) EIA or CIA with a high signal to cutoff ratio; or
    - ii) A positive RIBA; or
    - iii) A positive PCR?
- 6) If 'yes' to all of the above (5 a-c), the patient meets the acute Hepatitis C case definition, and the patient should be investigated by using the WVEDSS hepatitis form. Simultaneously submit paper copies of laboratory data. Educate the patient about hepatitis C.

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- a) Assure that cases are educated about hepatitis C transmission, prevention and control measures to prevent complications of hepatitis C such as:
  - i) Use of hepatitis A and B vaccines;
  - ii) Reduction or elimination of alcohol intake; and
  - iii) Referral for medical evaluation.
- 7) If the patient does not meet the acute case definition, complete the Hepatitis C Case Report form. If resources allow, educate the patient about hepatitis C. Document and return the completed form to IDEP.

### **Disease Prevention Objectives**

- 1) Prevent transmission of hepatitis C through education of persons who have tested positive for hepatitis C.
- 2) Reduce the incidence of acute hepatitis C through community education and programs to prevent drug use and sharing of needles.
- 3) Prevent nosocomial transmission of hepatitis C through effective infection control measures.
- 4) Prevent transmission of hepatitis C through screening of blood and organ donors.
- 5) Prevent complications of hepatitis C by assuring that persons with hepatitis C receive education about hepatitis A and B vaccines, and use of alcohol.

### **Disease Control Objectives**

- 1) Reduce transmission through timely identification and investigation of community-based and nosocomial outbreaks of hepatitis C so that appropriate control measures can be applied.

### **Surveillance Objectives**

- 1) Determine the incidence of acute hepatitis C in West Virginia.
- 2) Annually estimate the number of newly diagnosed cases of past or present hepatitis C in West Virginia.
- 3) Prospectively identify the risk factors associated with acute hepatitis C.

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- 4) Periodically identify the lifetime risk factors associated with chronic hepatitis C through special studies.
- 5) Identify demographic characteristics of persons with acute and chronic hepatitis C.
- 6) Periodically assess access to care and quality of care for patients with hepatitis C through special studies.

### **Public Health Significance**

Hepatitis C is a major cause of liver disease worldwide with an estimated prevalence of 2%, representing 123 million people. In the US, hepatitis C is the most common blood borne infection and causes up to 50 percent of cirrhosis, end-stage liver disease, and liver cancer. It is the most common reason for liver transplant. According to NHANES (National Health and Nutrition Examination Survey, 1988-1994), 1.8% of persons in the United States were infected with Hepatitis C. Sixty to 85 percent of HCV-infected persons develop chronic infection. The most important sequelae of chronic HCV infection are progressive liver fibrosis leading to cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). Estimates of the proportion of persons who develop chronic infection 20 years after exposure vary from 2 to 4 percent in children and young women, to 20 to 30 percent in middle-aged transfused subjects. There are 10,000 to 20,000 deaths attributed to HCV infection annually. Despite these statistics, most adults infected with hepatitis C have persistent viremia without evidence of liver disease. A minority of hepatitis C patients clear their infection spontaneously and a minority progress to severe disease.

Several cofactors are associated with accelerated progression to severe liver disease and complications: male gender, older age at acquisition, obesity, HIV coinfection, hepatitis B virus coinfection, liver disease from other causes, and alcohol consumption. Hepatitis C behaves like an opportunistic infection in persons with HIV infection. Patients with hepatitis B and C coinfection develop HCC at a higher rate. Patients who drink more than 50 grams of alcohol each day (4 or 5 drinks per day) have an increased rate of progression of liver fibrosis.

Hepatitis C is challenging for public health and medical professionals because the acute infection is often silent and the chronic infection can result in severe disease AND ongoing transmission. Surveillance must be as complete as possible, but laboratory surveillance may reflect only who is screened and not who is infected, and data reported with laboratory results are limited. At this time, there are no fully satisfactory methods for hepatitis C surveillance.

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### **Clinical Description**

Persons with acute hepatitis C are usually asymptomatic. About 25-30% of persons with acute hepatitis C will experience the classic symptoms of hepatitis, including malaise, anorexia, abdominal pain, jaundice, nausea, vomiting, diarrhea, etc. Acute hepatitis C is indistinguishable from acute hepatitis due to another virus. A full set of tests for viral hepatitis, including hepatitis A IgM, HBsAg, HBcIgM, and Hepatitis C EIA (with confirmation according to current guidelines) should be ordered, because of the frequency of coinfections. Acute hepatitis A superimposed on chronic hepatitis C infection can cause fulminant hepatitis.

An estimated 50-85% of HCV infected persons develop chronic infection. Again, most of these patients are asymptomatic, yet 2-4 % of children and young women and 20-30% of middle-aged transfused subjects may develop cirrhosis over a period of about 20 years. Persons with cirrhosis may develop edema, ascites, jaundice, bleeding or easy bruisability, loss of body mass, thinning of the skin, sleep disturbance, confusion, exhaustion, and loss of sexual drive or performance. Hepatocellular carcinoma is estimated to occur in about 1-4% of persons with cirrhosis every year.

### **Etiologic Agent**

Hepatitis C virus (HCV) is a 50 nm positive-stranded RNA virus. It is related to the genus Flavivirus (dengue and yellow fever).

### **Reservoir**

This virus is found only in humans. Chimpanzees and mice have been infected experimentally, but they play no known role in transmission to humans.

### **Mode of Transmission**

Hepatitis C is efficiently transmitted by the parenteral route. All injection drug users, even those who have used drugs only once, are considered to be at risk. Risk factors for transmission of HCV among drug users include: first-time use with an older user, frequent use, cocaine injection, and sharing of paraphernalia. Other important risk factors include: transfusion or organ transplantation, especially prior to July, 1992; hemodialysis; high-risk sexual activity; unsafe injections (in developing countries); occupational exposure to blood; and perinatal exposure.

Sexual transmission does occur, but is very inefficient. In the United States, the estimated seroprevalence of HCV is 2 to 3 percent among partners of HCV-infected persons who are in long-term monogamous relationships and is 4 to 6 percent among persons with multiple sex partners, sex workers, and men who have sex with men (those at risk for sexually transmitted diseases). One

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study found the risk of HCV infection to be threefold higher for female than male sexual partners. Therefore, sexual partners of male and female patients with hepatitis C may be offered testing for this infection. For heterosexual, discordant monogamous couples, the risk of transmission is estimated to be only 0 to 0.6 percent annually. However, HCV-infected individuals with multiple sexual partners or in short-term relationships should be advised to use condoms to prevent transmission of HCV and other sexually transmitted diseases.

The risk of perinatal transmission is approximately 2 percent for infants of anti-HCV seropositive women. When a pregnant woman is HCV RNA positive at delivery, this risk increases to 4 to 7 percent. Higher HCV RNA levels appear to be associated with a greater risk. HCV transmission increases up to 20 percent in women co-infected with HCV and HIV. There are no prospective studies evaluating the use of elective cesarean section for the prevention of mother-to-infant transmission of HCV. However, avoiding fetal scalp monitoring and prolonged labor after rupture of membranes may reduce perinatal transmission. Breast-feeding does not appear to transmit HCV. Infants born to HCV-positive mothers should be tested for HCV infection by HCV RNA tests on two occasions between the ages of 2 and 6 months and/or have tests for anti-HCV after 15 months of age. Positive anti-HCV in infants prior to 15 months of age may be due to transplacental transfer of maternal anti-HCV antibody.

Children and personnel should not be excluded from day care centers, schools, or sports on the basis of HCV infection. Standard (universal) precautions should be used in any situation where exposure to blood occurs.

Nosocomial transmission has rarely been reported. Dialysis patients are at increased risk for hepatitis C; probably because of unrecognized transmission during dialysis.

Transmission does not occur through casual contact (kissing, hugging, touching, coughing, sneezing, food, water, sharing eating utensils or drinking glasses, or other contact without exposure to blood etc.)

Healthcare workers have a similar or slightly lower prevalence of HCV infection than the general population, although they may have acquired their infection from occupational sources. Transmission from healthcare workers to patients has also been documented, but is rare and confounded by other risk factors. HCV-infected healthcare workers should use standard (universal) precautions to prevent transmission and should not be restricted from work.

The risk of HCV infection from a needlestick injury is estimated to be 2 percent. The source and exposed individual should be tested for antibody to HCV. If the source individual is HCV EIA positive, a RIBA or HCV RNA assay should be done in the exposed individual. Since HCV RNA is first detected in the blood 2 weeks after transmission, the exposed individual should be tested for HCV

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antibody, HCV RNA, and ALT at exposure and again between 2 and 8 weeks after injury. If seroconversion occurs, that person should be referred for consideration of treatment.

Body piercing and tattooing are other potential sources of transmission if contaminated equipment or supplies are used. However, transmission due to these activities is rare and confounded by other risk factors.

### **Incubation Period**

Incubation period is two weeks to six months; usually 6-9 weeks.

### **Infectious Period**

Persons with hepatitis C are infectious (viremic) from about two weeks after exposure for an indefinite period of time. Persons with chronic hepatitis C are intermittently viremic. Persons who test positive for hepatitis C should be assumed to be infectious unless repeated testing for hepatitis C RNA is documented to be negative.

### **Outbreak Recognition**

Outbreaks have been described in association with cardiac surgery, colonoscopy and outpatient surgery. If, two or more *acute cases* of hepatitis C occur in association with surgery, dialysis, another invasive procedure or another common source within the 2 week to 6 month incubation period, WVDHHR should be notified that a possible outbreak has been identified. Outbreaks have also been recognized in association with needle-sharing partners. Outbreak identification should be facilitated by use of the WVEDSS hepatitis investigation form to investigate acute cases of hepatitis C.

### **Case Definition for Acute Hepatitis C**

#### **2006 Case Definition**

#### **Clinical description**

An acute illness with a discrete onset of any sign or symptom consistent with acute viral hepatitis (e.g. anorexia, abdominal discomfort, nausea, vomiting), and

- a) jaundice, or
- b) serum alanine aminotransferase (ALT) levels >400 IU/L

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### **Laboratory criteria**

One or more of the following:

Anti-HCV screening-test-positive with a signal to cut-off ratio predictive of a true positive as determined for the particular assay as defined by CDC.

[http://www.cdc.gov/ncidod/diseases/hepatitis/c/sc\\_ratios.htm](http://www.cdc.gov/ncidod/diseases/hepatitis/c/sc_ratios.htm)

OR

HCV RIBA positive

OR

NAT for HCV RNA positive

AND

IgM antibody to hepatitis A virus (IgM anti-HAV) negative

AND

IgM antibody to hepatitis B core antigen (IgM anti-HBc) negative,

### **Case classification**

Confirmed: a case that meets the clinical case definition, is laboratory confirmed, and is not known to have chronic hepatitis C.

### **Case Definition for Viral Hepatitis C Infection (past or present)**

#### **2005 Case Definition**

#### ***Clinical description***

Most hepatitis C virus (HCV) infected persons are asymptomatic. However, many have chronic liver disease, which can range from mild to severe including cirrhosis and liver cancer.

#### ***Laboratory criteria for diagnosis***

- Anti-HCV positive (repeat reactive) by EIA, verified by an additional more specific assay (e.g. RIBA for anti-HCV or nucleic acid testing for HCV RNA), OR
- HCV RIBA positive, OR
- Nucleic acid test for HCV RNA positive, OR
- Report of HCV genotype, OR
- Anti-HCV screening-test-positive with a signal to cut-off ratio predictive of a true positive as determined for the particular assay (e.g.,  $\geq 3.8$  for the enzyme immunoassays) as determined and posted by CDC.

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### ***Case classification***

***Probable:*** a case that is anti-HCV positive (repeat reactive) by EIA and has alanine aminotransferase (ALT or SGPT) values above the upper limit of normal, but the anti-HCV EIA result has not been verified by an additional more specific assay or the signal to cutoff ratio is unknown.

***Confirmed:*** a case that is laboratory confirmed and that does not meet the case definition for acute hepatitis C.

### **Laboratory Diagnosis of Hepatitis C**

During acute infection, HCV RNA is first detectable within 1-3 weeks after exposure. The patient is viremic and potentially infectious at this time. Elevated ALT generally occurs at about 6-7 weeks after exposure, and the EIA becomes positive at about 6-12 weeks. Only 50-70% of individuals have a positive EIA at the onset of symptoms; 90% will seroconvert within 3 months.

Here are guidelines for interpretation of HCV test results, according to CDC recommendations (MMWR, February 7, 2003; Vol. 52(RR-3)).

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### Reference for Interpretation of HCV Test Results

If Your HCV Test Result Is:			Interpretation		Action
Anti-HCV Supplemental Test					
Anti-HCV Screening Test*	RIBA†	or HCV RNA	Anti-HCV	HCV Infection	Additional Testing or Evaluation
Negative	Not Needed	Not Needed	Negative	None	No
Positive	Not Done	Not Done	Not Known	Not Known	Supplemental Anti-HCV (RIBA) or HCV RNA
Positive	Not Done	Negative	Not Known	Not Known♦	Supplemental Anti-HCV (RIBA)
Positive (high s/co ratio‡)	Not Done	Not Done	Positive	Past/current	Evaluate for chronic infection and liver disease
Positive	Negative	Not Needed	Negative	None	No
Positive	Positive	Not Done	Positive	Past/current	Evaluate for chronic infection and liver disease
Positive	Positive	Negative	Positive	Past/current♦	Repeat HCV RNA
Positive	Positive/ Not Done	Positive	Positive	Current	Evaluate for chronic infection and liver disease
Positive	Indeterminate	Not Done	Indeterminate	Not Known	Test for HCV RNA or repeat Anti-HCV testing
Positive	Indeterminate	Positive	Indeterminate	Current	Evaluate for chronic infection and liver disease
Positive	Indeterminate	Negative	Negative	None	No

\* EIA- enzyme immunoassay or CIA- enhanced chemiluminescence immunoassay

† Recombinant immunoblot assay, a more specific anti-HCV assay

♦ Single negative HCV RNA result cannot determine infection status as persons might have intermittent viremia.

‡ Samples with high s/co ratios usually (>95%) confirm positive, but supplemental serologic testing was not performed. Less than 5 of every 100 might represent false-positives; more specific testing should be requested, if indicated.



Source: [http://www.cdc.gov/ncidod/diseases/hepatitis/resource/PDFs/hcv\\_graph.pdf](http://www.cdc.gov/ncidod/diseases/hepatitis/resource/PDFs/hcv_graph.pdf)

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Signal to cut off ratio is an adequate cost-effective alternative for confirmation of a positive laboratory screening test in persons who are not candidates for treatment of hepatitis C. CDC maintains a listing of signal-to-cut-off ratios for screening tests at:

[http://www.cdc.gov/ncidod/diseases/hepatitis/c/sc\\_ratios.htm](http://www.cdc.gov/ncidod/diseases/hepatitis/c/sc_ratios.htm)

Screening test signal-to-cut-off ratios appropriate for licensed tests:

Screening test kit	Signal-to-cut—off ratio predictive of a true positive ≥ 95% of the time
Ortho HCV Version 3.0 ELISA Test System	3.8
Abbott HCV EIA 2.0	3.8
Ortho Vitros Anti-HCV Assay	8
Abbott AxSYM Antibody to HCV	10
Bayer Advia Centaur HCV Assay	Not Yet Available

Laboratory testing is available at the Office of Laboratory Services. For information click on:

<http://www.wvdhhr.org/labservices/> or call 304-558-3530.

### **Preventive Interventions**

*For persons who are HCV-positive, share the following information:*

1. Don't donate:
  - ☐ Blood;
  - ☐ Body organs or other tissue; or
  - ☐ Semen.
2. Don't share personal items, including:
  - ☐ Toothbrushes or dental appliances;
  - ☐ Razors; or
  - ☐ Nail-grooming equipment.
3. Cover cuts or skin lesions.
4. Stop using or injecting illegal drugs. Enter and complete substance abuse treatment, including relapse prevention. If still injecting, follow risk reduction practices (See below).
5. Consult a physician regarding treatment. Some people benefit from treatment. Additional testing may be required to determine if treatment will be beneficial, including blood tests and a liver biopsy. Be sure to select a physician who is knowledgeable about hepatitis C.
6. Stop drinking alcohol or drastically reduce consumption.
7. Get immunized against hepatitis A.
8. If using drugs or engaged in high-risk sexual activity, get immunized against hepatitis B.
9. Counseling regarding sexual behavior:

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- a. For persons who have only one sex partner: While it is advisable to inform that partner, no change in sexual practices is necessary. Risk of transmission is about 1%.
- b. For persons who have multiple partners: Reduce the number of partners. Inform all partners of their status and use latex condoms. Risk of transmission is approximately 5 to 10%.

Risk reduction practices -- *For persons regardless of serostatus who are still using drugs:*

- ☐ Never reuse or share syringes, water, or preparation equipment.
- ☐ Use only syringes obtained from a reliable source. In West Virginia, syringes can be obtained without a prescription at veterinary supply stores.
- ☐ Use a new sterile syringe to prepare and inject drugs.
- ☐ Use sterile water to prepare drugs. If sterile water is not available, clean tap water is preferable to water from other sources.
- ☐ Use a new or disinfected container ('cooker') and a new filter ('cotton') to prepare drugs.
- ☐ Clean the injection site with a new alcohol swab prior to injection
- ☐ Safely dispose of syringes after one use.

### **Postexposure Prophylaxis and Follow-Up**

The prevention of HCV infection with immunoglobulin (IG) is not effective for postexposure prophylaxis of hepatitis C. There is no vaccine available for hepatitis C.

### **Treatment**

Treatment is an individual decision recommended for persons who are likely to benefit. Selection of persons likely to benefit requires an evaluation, including:

1. Confirmation of the diagnosis.
2. Review of medical history and laboratory studies to identify possible contraindications to therapy
3. Viral load testing
4. Genotyping
5. Liver biopsy in selected patients

Pegylated interferon and ribavirin are used for treatment. For more information, see: Gastroenterol, 2006; 130:231-64 or other current medical literature.

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### Surveillance Indicators

- Proportion of acute cases of hepatitis C with complete demographic information
- Proportion of acute cases of hepatitis C with complete information on risk factors
- Proportion of acute cases of hepatitis C who have been educated.
- Proportion of chronic cases of hepatitis C with complete demographic and locating information.

### References

- 1) Centers for Disease Control and Prevention. 'Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus.' MMWR, 2003; 52(No RR-3).
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- 3) Dienstag J L, and McHutchison J G. 'American Gastroenterological Association technical review on the management of hepatitis C.' Gastroenterol, 2006; 130:231-64.
- 4) Laurer G M and Walker B D. 'Hepatitis C virus infection.' New Engl J Med, 2001; 345:41-52.
- 5) Patel K, Muir AJ, McHutchinson JG. 'Diagnosis and treatment of chronic hepatitis C infection' BMJ, 2006; 332:1013-1017.
- 6) Seef LB, Miller RN, Rabkin CS, et.al. '45-year follow-up of hepatitis C virus infection in healthy young adults.' Ann Intern Med, 2000; 132:105-111.
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- 8) Thomas D L, Astemborski J, Rai RM, et.al. 'The natural history of hepatitis C virus infection: Host viral and environmental factors.' JAMA, 2000; 284:450-456.
- 9) Wong T, Lee SS. 'Hepatitis C: a review for primary care physicians.' CMAJ, 2006; 174:649-659.

### Websites

- 1) Centers for Disease control and Prevention: <http://www.cdc.gov/ncidod/diseases/hepatitis/>
- 2) National Institutes of Health: [http://digestive.niddk.nih.gov/ddiseases/pubs/hepc\\_ez/](http://digestive.niddk.nih.gov/ddiseases/pubs/hepc_ez/)  
<http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc/>
- 3) American Liver Foundation: <http://www.liverfoundation.org/>